REMARKS

Claims 1-25 are pending in the present application. No new claims fees are due.

The specification has been amended to correct a typographical error wherein a methyl ester intermediate is presented where it is clear from the previous formulae and the context of the specification, an ethyl ester was intended. This amendment is not made for reasons of patentability nor in view of the prior art, but only to correct a typographical error.

Claim 11 has been amended to correct the same formula error as which occurs in the specification. Claim 11 has also been amended to correct one or more typographical errors.

Rejection under 35 USC § 112

The Examiner has rejected Claims 8 and 11-25 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claiming the subject matter which applicant regards as the invention.

The amendment to Claim 8, correcting the typographical error, obviates the Examiner's rejection to Claim 8.

The amendment to Claim 19, correcting the typographical error, obviates the Examiner's rejection to Claim 19.

Claim 11 has been amended to correct the formula. It is clear the ethyl ester was intended, both as a fact from the precursors and final product, as well as the accompanying text. Claim 11 has also been amended to correct the typographical error changing the word "agents" to "agent."

The Examiner asserts that the term "Knoevenagel Reaction adduct" is inapt. The Examiner's attention is drawn to the specification at page 11, line 20 which recites: [s]tep (b) of the present invention relates to the reaction of the admixture formed in Step (a) with an adduct which is capable of undergoing a Knoevenagel or Knoevenagel-like reaction..." This is clearly antecedent basis for the phrase "a Knoevenagel Reaction adduct."

The amendments to the Claims are amendments to correct typographical errors and are not made for reasons of the prior art nor are they made in any regard to issues of patentability.

Reconsideration and withdrawal of the rejection to Claims 8 and 11-25 under 35 USC § 112 is therefore respectfully requested.

Rejection under 35 USC § 103(a)

The Examiner has rejected Claims 1-25 under 35 USC § 103(a) as allegedly obvious over U.S. 5,703,231 Randall et al., issued December 30, 1997 (hereinafter "Randall '231") in view of

U.S. 4,695,646 Maurer et al., issued September 22, 1987 (hereinafter "Maurer '646"). The Examiner's rejection is respectfully traversed.

The courts have ruled:

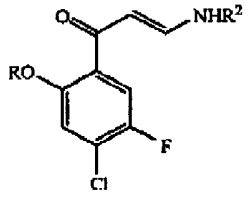
> In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification. ***In re Lintner*, 173 USPQ 560, 562 (C.C.P.A. 1972).**

The court has subsequently added that the reference teachings:

> Appear to have suggested the *claimed subject matter*. ***In re Rinehart*, 189 USPQ 143, 147 (C.C.P.A. 1976).** (emphasis added)

Therefore, *ab initio*, the Examiner must show the present claims are suggested by the combination of Randall '231 and Maurer '646.

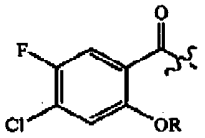
A first question which must be satisfactorily answered is whether the cited prior art is analogous art and whether the problem solved therein is related to or is applicable to the problem solved by the present invention. Maurer '646 relates to the preparation of amino acrylic acid derivatives having the formula: 11



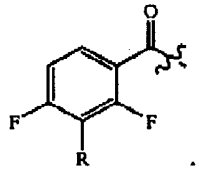
wherein R is short chain alkyl. Maurer '646 sets forth the object of his invention at column 1, line 15, and each of these objectives relates to a single product form; aryl ketones having the 2-alkoxy-4-chloro-5-fluorophenyl scaffold. This substitution pattern is unique to itself and key to the invention of Maurer '646. It is the only assembly of atoms which is taught by Maurer '646; no other arrangement of atoms along an aryl ring is suggested.

Maurer '646 is directed to an improved process for preparing the known 4-oxo-quinoline antibacterial agents, *inter alia*, 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydroquinoline-3-carboxylic acid (compounds which are disclosed in EP 0 078 362), and the improvement lies in the use of the Maurer '646 compounds as intermediates to make these agents. Therefore, Maurer '646 only encompasses the 2-alkoxy-4-chloro-5-fluorophenyl scaffold and the disclosure does not suggest anything beyond that scope.

As it relates to the difference between the compounds of Maurer '646 and the present invention, it is well understood by those of ordinary skill in the art that the substitution pattern on an aryl ring, especially a phenyl ring, influences the reactivity of the core ring. The Maurer '646 parent ring has the formula:



whereas the ring system of the present invention has a different substitution pattern; one having the formula:



These scaffolds are clearly not the same. The reactivity imbued in the scaffold of Maurer '646 is unique to that alignment and ring substituents. In fact, the disclosure of Maurer '646 implies this fact since the disclosure of Maurer '646 is limited to a single scaffold; 2-alkoxy-4-chloro-5-fluorophenyl. The courts have recognized the criticality of structural changes, even ones which are more subtle than the present case. It is therefore well settled that when drafting and claiming a chemical-related invention, there is a burden on the patentee to limit his description to the operable subject matter: 12

> [a chemical species] "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. ***University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997)** (quoting ***Fiers*, 25 USPQ2d at 1606)**

Going beyond what is known and what is clearly outside the scope of the invention risks imbuing upon a composition of matter a number of imaginary properties. Thus, in exchange for requiring this specific calling out of the subject matter of the invention, applicants for a chemical-related patent have been provided the following relief by the courts:

> [S]tructural similarity alone is not sufficient to establish obviousness. ***Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 2001 U.S. Dist LEXIS 18361 at 24 (S.D. Ind. 2001).**

In his rejection, the Examiner states:

> Thus it is shown that alkoxy is a common leaving group in this quinolone forming cyclization and thus one of ordinary skill would have been motivated to use ethoxy as the leaving group in the Randall et al. process.

The Examiner has erred in his conclusion and in his understanding of what the courts have ruled is proper to construe from the prior art. Maurer '646 doesn't teach alkoxy is a common leaving group, it only teaches alkoxy is a suitable leaving group for a specific alignment of substituents on a phenyl ring; i.e., 2-alkoxy-4-chloro-5-fluorophenyl. Finding one example of alkoxy, asserting it is therefore "common" is not proper and wholly insufficient to establish a case of obviousness under 35 USC §103(a).

In ***In re Tomlinson*, 150 USPQ 623 (C.C.P.A. 1966)** the court considered the patentability of an invention directed to polypropylene stabilized with a particular class of dithiocarbamate. The prior art disclosed polyethylene stabilized with these same dithiocarbamate compounds. The court summarized:

> The Patent Office analysis of this art and conclusion as to what would be suggested thereby to one of ordinary skill in the art can be summarized thus: Polyethylene is "closely related" to polypropylene. One skilled in the art, accordingly, would expect an ultraviolet light stabilizer for polyethylene to be effective as an ultraviolet stabilizer in polypropylene.

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The court stated in overturning the PTO's rejection ***Id.*** at 626:

> [A]ppellant's invention is the *discovery* of *what* stabilizers for other materials, known in the art, *will* and which *will not* stabilize *polypropylene*...(emphasis in original)

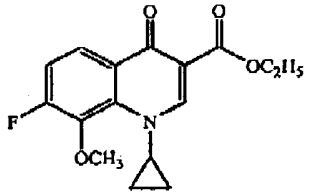
Likewise the present invention is the discovery of which leaving groups (especially one formed as a potentially unwanted by-product), known in the art, will be effective in forming the 4-oxo-quinoline ring system of the desired product. It is, therefore, well decided that the motivation to modify a reference must come from the prior art and not from the applicant's disclosure. The standard of "obvious to try" is not sufficient to form a rejection of obviousness under 35 USC §103(a).

The Federal Circuit has repeatedly warned that the requisite motivation must come from the prior art, not Applicant's specification. It is, therefore, improper to:

> **[use] that which the inventor taught against its teacher. *In re Lee*, 277 F.3d at 1343 citing *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir 1988).**

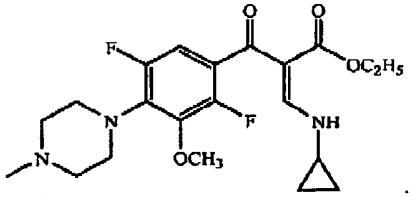
Randall '231 relates to a process for making antimicrobial compounds and serves to establish the state of the art as it relates to the synthesis of quinolone ring scaffolds. The Examiner's attention is drawn to the first 14 examples wherein the 2,4,5-trifluorophenyl ring adduct predominates. Indeed, in all of the examples for forming the core quinoline ring scaffold, the 4-position of the parent phenyl ring is substituted by an amino unit, *inter alia*, 4-methyl piperazine.

Randall '231 differs substantially from the process of the present invention. In the present case, a final product is formed which can be reacted with one or more adducts at the 7-position of the final quinoline scaffold (the original 4-position), for example:



wherein the 7-position fluorine atom serves as a suitable leaving group. The present process takes advantage of the fact there is no activated 6-position fluorine atom on the final quinoline scaffold as there is on the final quinoline ring scaffold of Randall '231.

Randall '231 discloses a process wherein the 4-position of the quinoline ring precursor (phenyl ring) has been substituted by a 4-methylpiperazine ring, *inter alia*, and therefore it is left unknown what effects on the Randall '231 ring system the process steps of the present invention would have. Prior to ring closure the Randall '231 adducts have a formula such as: 14

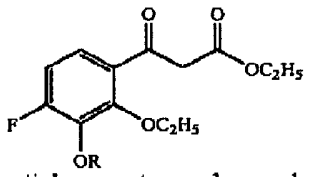


This is in stark contrast to the process of the present invention which leaved a fluorine atom at the 7-position of the quinoline ring. The courts have ruled:

> There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure. ***In re Dow Chem. Co.*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988).**

The sequence of steps in Randall '231 and the present invention are not even the same. The only sequence disclosed in Maurer '646 is the ring closure sequence copied from the prior art, i.e. EP 0 078 362. Maurer '646's invention *stops* before the ring closure sequence!

There is no suggestion in Randall '231 that an impurity is produced during the formation of the core aryl β-ketoester. And this is the heart of the present invention. The present specification reads beginning at page 6, line 20:

> It has now been surprisingly discovered that the presence of an impurity having the general formula:
>
> 
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>
> which is formed in substantial amounts as a by product of the reaction of 3-substituted 2,4-difluourbenzophenones with diethylcarbonate, can be successfully cyclized, together with the corresponding 2-fluoro adduct...

Nowhere in the disclosure of Maurer '646 or Randall '231 is there a teaching that by-products are formed in the reactions leading up to the point of ring closure. Therefore, the problem solved by the present invention is not known in either of the prior art references. The CCPA has held:

> A patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. **In re Sponnoble 612 F.2d at 1290, 204 USPQ at 837**:

Indeed, when this ruling is taken together with the instructions of the Federal Circuit:

> The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. ***In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989)**

It becomes clear that the Examiner has not met his burden to find motivation to modify the prior art reference and thereby render the present invention obvious. Therefore, not only was the problem solved by the present invention not known, but there is no suggestion to modify Maurer '646 to solve the problem of the present invention.

In summary, Maurer '646 is not a proper prior art reference because it deals solely with reactions on an aryl ring having a particular substitution pattern, and because each substituent along an aryl ring has profound effects on the nature and reactivity of the ring, the teachings of Maurer '646 are directed only to a particular aryl ring system. The present process, however, does teach and suggest that where a problem is encountered similar to that disclosed in the present specification, the remedy lies in the solution taught by the Applicant. And Randall '231 does not teach nor suggest the problem described in the present invention existed. Therefore, Randall '231 is not proper prior art over the present invention.

In light of the herein above arguments, reconsideration and withdrawal of the rejection to the Claims under 35 USC § 103(a) is therefore respectfully requested.

CONCLUSION

Applicants have made an earnest effort to place the present claims in condition for allowance. WHEREFORE, entry of the amendments provided herewith, reconsideration of the claims as amended in light of the Remarks provided, withdrawal of the claims rejections, and allowance of Claims 1-25, as amended, are respectfully requested. In the event that issues remain prior to allowance of the noted claims, then the Examiner is invited to call Applicants' undersigned agent to discuss any remaining issues.

Respectfully submitted,

By _____

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April 26, 2004
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